REMARKS/ARGUMENTS

Claims 1-13 are pending. Claims 3 and 9 are withdrawn due to restriction requirement. Claims 1, 2, 4-8 and 10-13 are rejected. Claim 1 is canceled. New claims 14-19 are added.

Support for amendment of claims 2 and 8 can be found, e.g., in the paragraph spanning pages 12-13 (obtained from or synthesized from a nucleic acid obtained from), and at page 11, lines 6-14 and in the paragraph spanning pages 35-36 (obtained from an organ affected by the disorder). Support for amendment of claims 7 and 13 can be found, e.g., in the paragraph spanning pages 12-13. Support for new claims 14 and 15 can be found, e.g., at p. 10, lines 21-35. Support for new claims 16 and 17 can be found in original claim 2 and in the paragraph spanning pages 35-36. Support for new claims 18-19 can be found at p.37, lines 8-24. Amendment of the claims should not be construed as acquiescence in the rejections.

Elections/Restrictions

Applicants maintain traverse of the restriction requirement for the reasons stated previously.

Priority

The Examiner has granted priority only as far as the filing date of the PCT/JP00/06313 application on the basis that Applicants have not provided an English translation of the priority documents. Applicants note that according to the MPEP, English translations of the priority documents may only be required by the Examiner when there is an intervening reference, which is not the case here:

> The only times during ex parte prosecution that the examiner considers the merits of an applicant's claim of priority is when a reference is found with an effective date between the date of the foreign filing and the date of filing in the United States and when an interference situation is under consideration....In those cases where the applicant files the foreign papers for the purpose of

> overcoming the effective date of a reference, a translation is required if the foreign papers are not in the English language.
>
> MPEP § 201.15

Both references cited by the Examiner predate the earliest priority document. The Examiner therefore need not make any comment on whether Applicants are entitled to the claimed priority date.

Drawings

The Examiner has objected to an unidentified Figure for failing to identify a sequence. Applicants presume this is an objection to Figure 1. Attached herewith is a corrected Figure 1 containing a reference to SEQ ID NO: 4.

Claim Objections

The Examiner has objected to Claims 1, 4-7, and 10-13 for reciting non-elected subject matter. Claim 1 has been canceled. Claims 4, 5, 10, 11 and 13 have been amended to remove reference to non-elected subject matter. Dependent claims 6, 7 and 12 no longer recite non-elected subject matter due to amendment of claims 5 and 11.

35 U.S.C. § 112, first paragraph

Claim 1 has been rejected as not enabled. Claim 1 has been canceled.

35 U.S.C. § 112, second paragraph

Claims 1, 2, 4-8 and 10-13 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Examiner says that the term "nucleic acid derived from" is indefinite.

Claim 1 has been canceled. Independent claims 2 and 8 have been amended to recite "a nucleic acid obtained from or synthesized from a nucleic acid obtained from a tissue of an organism..." This amendment clarifies the scope of the nucleic acids recited in claims 2 and 8 by specifying that the nucleic acids are either (a) obtained from a tissue; or (b) synthesized

from a nucleic acid obtained from a tissue. "Synthesized from" refers to nucleic acid molecules that, for example, are clones contained in vectors created from the actual nucleic acids obtained from a tissue, as well as nucleic acids synthesized using PCR amplification of the actual nucleic acids obtained from a tissue. These examples of nucleic acids synthesized from the actual nucleic acids obtained from a tissue are described in the paragraph spanning pages 12-13. Applicants note that this paragraph concludes by citing Sambrook et al., which contains a large number of examples of propagating clones in vectors, as well as an entire chapter on PCR (Chapter 14). As amended, the scope of claims 2 and 8 is clear to a person skilled in the art.

Claims 1, 2, 4-8 and 10-13 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Examiner says that the term "tissue is derived from" is indefinite. The same claims are also rejected for reciting "the vicinity of the affected area."

Claim 1 has been canceled. Claims 2 and 8 have been amended to recite "tissue is obtained from an organ affected by the disorder." This amendment clarifies claims 2 and 8 by specifying that the tissue used to isolate nucleic acids for testing is obtained from an organ affected by the disorder. These amendments are supported by page 11, lines 6-14. An example of a tissue obtained from an organ affected by a disorder can be found in the paragraph spanning pages 35-36, which describes removing a sample of cells from the brain (an organ) of a patient suffering from a disorder (Alzheimer's disease). As amended, the scope of claims 2 and 8 is clear to a person skilled in the art.

Claims 1, 2, 4-8 and 10-13 have been rejected for failing to recite a positive process step which recapitulates the preamble of the claimed method. Claim 1 has been canceled. Claims 2 and 8 have been amended to recite such a positive process step as suggested by the Examiner.

35 U.S.C. § 102(b)

The Examiner has rejected claims 1, 2, 4-8 and 10-13 as anticipated by Giambarella and Guo. The Examiner says that both of these references teach every limitation as set forth in the claims, and therefore anticipate the claimed invention. The Examiner has interpreted "a nucleic acid derived from a tissue" to mean any nucleic acid. The Examiner has

also interpreted a "tissue derived from an area affected by a disorder" to mean any tissue culture system comprising cells that exhibit the characteristics of a disorder that accompanies cell death. The anticipation rejection is respectfully traversed insofar as it might be applied to the amended claims.

Claims 2 and 8 have been amended to recite "a nucleic acid obtained from or synthesized from a nucleic acid obtained from a tissue of an organism suffering from a disorder that accompanies cell death, wherein said tissue is obtained from an organ affected by the disorder...." Applicants point out the significantly different scope of the amended claim terms compared to the interpretations the Examiner has used in the Office Action. First, the nucleic acid recited in the amended claims is obtained from or synthesized from a nucleic acid obtained from a tissue of an organism that has been obtained from an organ affected by a disorder. This amended language is narrower than the Examiner's interpretation of the canceled version of this term to mean "any nucleic acid." Second, the tissue recited in the claims is obtained from an organ affected by a disorder. This amended language clarifies the source of the tissue and has a different scope from the "tissue culture system comprising cells that exhibit the characteristics of a disorder that accompanies cell death" that the Examiner has used in the interpretation of the canceled version of this term.

Giambarella discusses expression of a Familial Alzheimer's Disease (FAD) gene, APP, in COS cells. Expression of the V642I mutant of the APP gene in COS cells induces apoptosis. Giambarella also discusses co-expression of APP V642I and a carboxy terminal fragment of the ß-adrenergic receptor kinase-1 (ßARK1) gene. Giambarella discusses attenuation of apoptosis in cells co-expressing APP V642I and ßARK1 but not in cells that only express APP V642I. Giambarella sets forth a highly detailed hypothesis for the selection of ßARK1 as a possible suppressor of apoptosis:

> These observations suggest that APP has not only the structure but also the function of a cell surface receptor. Our own earlier study...found that APP_{695} has an intrinsic G_o-stimulating domain at His657-Lys676 and forms a complex with G_o through this cytoplasmic domain. It has been confirmed that the synthetic His657-Lys676 peptide activates G_o in vivo...We subsequently indicated that intact APP_{695} causes activation of G_o through

> His657-Lys676 in response to anti-APP monoclonal antibody in reconstituted vesicles...Therefore, APP_{695} has a molecular function as a G_o-coupled receptor. G_o is a heterotrimeric G protein that serves as a signal transducer in vivo; thus, APP_{695} may play a role as a signaling receptor...
>
> paragraph spanning pages 4897-4898

Giambarella then discusses the possible role of G_o in apoptosis:

> Significantly, G_o has been implicated in apoptosis after transfection of NK1 cells with the three FAD mutants...[first sentence of second full paragraph on page 4898]...Based upon these multiple lines of evidence, we have concluded that the three FAD-linked mutants of APP activate G_o and thereby induce apoptosis in these cells. [first sentence of last paragraph on page 4898]

Giambarella then discusses specific G_o subunits, ßARK1, and a hypothesis:

> G_o belongs to the oligomeric G protein family, which consists of two functional subunits, Gα and Gßγ...Therefore, it is essential to know which subunit of PTX-sensitive G-protein G_o is responsible for the induction of apoptosis triggered by the V642 mutants of APP in NK1 cells...[from first full paragraph of page 4898, column 2] Our strategy was to examine...whether the isolated Gßγ-binding domain of ßARK1, an established Gßγ inhibitor, attenuates apoptosis...[from last paragraph of page 4898, column 2]

Guo discusses expression of an Alzheimer's associated gene, Presenilin 1 (PS-1) in PC12 cells. Guo discusses increased vulnerability to apoptosis induced by the Alzheimer's associated peptide Aß in PC12 cells expressing FAD-associated mutant forms of PS-1. Guo also discusses attenuation of apoptosis in PC12 cells expressing FAD-associated mutant forms of PS-1 that also express the calcium-binding protein calbindin D28k. Guo sets forth a detailed hypothesis for the selection of calbindin as a possible suppressor of apoptosis:

> Increased oxidative stress and disruption of neuronal calcium homeostasis appear to be interrelated final common pathways that mediate the neurodegenerative process in AD... Studies of postmortem AD brain revealed evidence for calcium-mediated proteolysis in degenerating neurons and suggest an inverse relationship between expression of calcium-binding proteins in

> neurons and their vulnerability to death. Cell culture studies have shown that the mechanism of Aß toxicity involves excessive accumulation of calcium within neurons and that calcium influx can elicit cytoskeletal alterations similar to those seen in neurofibrillary tangles in AD. Expression of the calcium-binding protein calbindin D28k in cultured hippocampal neurons is correlated with increased resistance to cell death induced by a variety of insults including exposure to Aß.
>
> page 3227, second column

Giambarella and Guo both lack an element of the amended claims. Neither reference contains the element of a nucleic acid obtained from or synthesized from a nucleic acid obtained from a tissue of an organism suffering from a disorder that accompanies cell death, wherein the tissue is obtained from an organ affected by the disorder. This element is recited in remaining independent claims 2 and 8 as amended.

In both references, the nucleic acid used to suppress cell death was selected based on highly detailed hypotheses that were developed based on the known biochemical properties of the proteins they encode. Both Giambarella and Guo set forth logical, hypothesis-driven rationales for why expression of ßARK1 and calbindin, respectively, could potentially suppress apoptosis in cell lines expressing FAD-associated genes. The actual source of these genes is not a tissue of an organism suffering from a disorder that accompanies cell death. Rather, the source of the ßARK1 gene is referenced as being "kindly provided by Dr. R.J. Lefkowitz." (Giambarella, p.4904, second column, last paragraph). The source of the calbindin gene is not disclosed in Guo, which simply states:

> PC12 cell lines stably expressing calbindin D28k were established by transfection with an expression vector containing the rat calbindin D28k cDNA subcloned into the pREP4 expression vector (Invitrogen) in which expression is under the control of Rous sarcoma virus long terminal repeat promoter.
>
> Guo, p.3228, first column, first full paragraph

Giambarella and Guo do not disclose the element of a nucleic acid obtained from or synthesized from a nucleic acid obtained from a tissue of an organism suffering from a disorder that accompanies cell death, wherein the tissue is obtained from an organ affected by the disorder. In the absence of this element, neither Giambarella nor Guo anticipates the claims as

amended. Because the cited references do not anticipate the methods of the recited claims, Applicants respectfully request that the anticipation rejection be withdrawn.

Neither reference would have rendered the claims obvious. The discussions of both references teach directly away from the instant claims because they suggest that expression of a specific gene with a known biochemical activity that counteracts a cell death-associated pathway is the way to identify genes that attenuate cell death. The teachings of Giambarella and Guo would not have motivated a practitioner to make a cDNA library using a tissue sample taken from an organ affected by a cell death disorder and screen millions of distinct gene sequences for the desired activity because these references suggest that the way to attenuate cell death is to express genes that have a known function which could counteract known biochemical pathways related to cell death.

Giambarella sets forth a highly detailed hypothesis for why an inhibitor of a particular subunit of a heterotrimeric G protein complex could attenuate cell death. This hypothesis begins on p.4897 in the second full paragraph, starting with a proposal that the APP gene product is a cell surface receptor. The discussion and hypothesis, excerpts of which are quoted above, continues through a highly detailed explanation of the G_o complex and culminates at the bottom of the second column of page 4898. Specifically, point (iii) in the last paragraph on p. 4898 suggests that co-expression of ßARK1 could attenuate cell death. In like manner, Guo describes characteristics of FAD-gene-induced cell death and sets forth a detailed hypothesis for why modulating calcium homeostasis through coexpression of calbindin could attenuate cell death. This discussion is found in the second column of p.3227 of Guo.

The teaching of Guo suggests that any gene that encodes a protein that contains a consensus "EF-hand" calcium binding domain is a candidate for attenuating cell death. Following this teaching, a practitioner would select other genes besides calbindin based on either known calcium binding properties or the presence of an EF-hand domain in the selected gene. Likewise, a practitioner would select other genes besides ßARK1, following the teaching of Giambarella, based on the known or suspected property of binding a subunit of the G_o complex. The teachings of Giambarella and Guo would not motivate a practitioner to make a cDNA library consisting of unknown gene sequences and assay the sequences for attenuation of cell

death. The cited references teach away from such an approach because, unlike ßARK1 and calbindin, the likelihood that any gene from the cDNA library attenuates cell death is extremely low.

The instant claims recite a method that is diametrically opposite to that discussed in Giambarella and Guo. The instant claims recite methods of screening for a disorder suppressor gene (claim 2) and methods for testing a suppressive effect of a nucleic acid on a disorder (claim 8). Both methods do not require any *a priori* knowledge of the identity or function of genes obtained from the recited source. Instead, as example 1 discloses, the claimed methods work by the isolation of nucleic acids from an organ affected by a disorder followed by screening. Unlike the cited references, which each test co-expression of one (Guo) or several (Giambarella) hypothesis-based genes, the library disclosed in Example 1 contained approximately 3.2 million independent clones (p.36, lines 12-14). These clones were screened for the ability to attenuate cell death, as disclosed at p.37, lines 8-24. The screening of clones was performed three times, and plasmids from independent surviving cell clones were cross hybridized to identify redundant clones. Only after narrowing the clones into non-redundant groups did the inventors actually examine the sequence of the clones that impart the cell death attenuation phenotype. Nothing in Giambarella and Guo suggests performing the recited methods. In fact, the highly detailed hypotheses of Giambarella and Guo teach directly away from the approach disclosed in the specification because they suggest that the way to attenuate cell death is to express genes that have a known function which could counteract known biochemical pathways related to cell death. The cited references therefore would have provided no motivation to perform the methods recited in the instant claims.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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